ABSTRACTS

Gregory L. Moneta, MD, Abstracts Section Editor

Growth rate and associated factors in small abdominal aortic aneurysms

Vega de Ceniga M, Gomez R, Estallo L, et al. Eur J Vasc Endovasc Surg 2006;31:231-6

Conclusion: Growth rates of small abdominal aortic aneurysms (AAAs) increase with the baseline size of the aneurysm. Both diabetes and chronic limb ischemia reduce growth rate of small AAAs.

Summary: This was a longitudinal, observational, prospective study to evaluate growth rates of small AAAs and factors that may influence growth. Patients with AAAs <5 cm in diameter were divided into two groups by a baseline ultrasound examination. Group I patients had aneurysms between 3 and 3.9 cm (n = 246), and group II patients had aneurysms between 4 and 4.9 cm (n = 106). Patients in group I underwent annual ultrasound scans, and patients in group II underwent CT scans every 6 months. There were 352 patients (333 men and 19 women) monitored for a mean of 55.2 ± 37.4 months (range, 6.3 to 199.8 months).

Aneurysm growth rate was greater in patients in group II (4.72 ± 5.93 mm/y vs 2.07 ± 3.23 mm/y; $P < 0.0001$). During follow-up, 87 patients (24.7%) died. One patient died because of a ruptured AAA and one died during elective aneurysm repair. Two aneurysms ruptured in group II: one had expanded to 5.6 cm, and the second had expanded to 6 cm. Rapid expansion (defined as >4 mm/y) was more prevalent in group II than group I (36.8% vs 13.8%; $P < .0001$). No expansion (0 mm) was observed in 17.9% of patients in group II and 25.2% of patients in group I ($P = .14$). During the follow-up period there were 36 patients (14.6%) in group I where the aneurysm grew to 5 cm in diameter, and there were 72 patients (67.9%) in group II where the aneurysm reached 5 cm in diameter (odds ratio 12.35; 95% confidence interval, 7.19 to 21.28; $P < .0001$).

Cardiovascular risk factors did not influence growth rate in group I. Diabetic patients in group II had significantly lower growth rates than nondiabetic patients (1.69 ± 3.51 vs 5.22 ± 6.11 mm/y; $P = .032$). Chronic limb ischemia was associated with slower aneurysm expansion (odds ratio 0.47; 95% confidence interval, 0.22 to 0.99; $P = .045$).

Comment: There are no major surprises here. Small aneurysms rupture very infrequently, and larger small aneurysms grow faster than smaller small aneurysms. The differential affects of cardiovascular risk factors on growth rate of aneurysms, although previously shown, is perhaps not as well appreciated. The UK Small Aneurysm Trial also demonstrated decreased growth rates of aneurysms in patients with peripheral arterial disease and in patients with diabetes (Circulation 2004;110:16-21). Observations with respect to peripheral arterial disease and diabetes on growth rate of small AAAs observed in this study are therefore unlikely the result of chance. There may be changes in the collagen vs elastin content of the aortic wall in patients with diabetes or in those whose atherosclerotic risk factors have produced both occlusive as well as aneurysmal disease.

Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial

Missen FE, Nicholls SJ, Sipahi I, et al, and the ASTEROID Investigators. JAMA 2006;295:1556-65

Conclusion: Very-high-intensity statin therapy with rosuvastatin can reduce coronary atherosclerosis as assessed by intravascular ultrasound (IVUS).

Summary: The authors performed a prospective, open-labeled, blinded end point trial to determine the effect of very-high-intensity statin therapy on coronary atherosclerosis as assessed by IVUS. The study was conducted in 53 community and tertiary medical centers in the United States, Canada, Europe, and Australia. Coronary atheromas were assessed at baseline and after 24 months of treatment. A total of 507 patients had a baseline IVUS examination and received at least one 40-mg dose of rosuvastatin a day. There was no placebo arm of the trial, with all patients receiving 40 mg/d of rosuvastatin. At 24 months, 349 patients had an evaluable IVUS examination. Primary efficacy parameters were a change in atheroma volume percentage measured by IVUS and change in atheroma volume in a 10-mm subsegment of artery with the greatest disease severity at baseline. A second efficacy variable was normalized atheroma volume for the entire artery.

At baseline, the mean low-density lipoprotein cholesterol (LDL) was 130.4 ± 34.3 mg/dL. This declined to 60.8 ± 20.0 mg/dL with treatment with rosuvastatin, a mean reduction of 53.2% ($P < .001$). The mean high-density lipoprotein cholesterol (HDL) level at baseline was 43.1 ± 11.1 mg/dL. This increased to 49.0 ± 12.6 mg/dL with rosuvastatin treatment, an increase of 14.7% ($P < .001$). The mean change in the percentage of atheroma volume was −0.98% ± 3.15% with a median of −0.79% (97.5% confidence interval [CI], −1.21% to −0.53%), $P < .001$ compared with baseline. The mean change in atheroma volume in the most diseased 10-mm subsegment was −6.1 ± 10.1 mm^3, with a median change of −5.6 mm^3 (97.5% CI, −6.8 mm to −.40 mm^3), $P < .001$ compared with baseline. Total atheroma volume showed a 6.8% median reduction, with a mean reduction of −14.7 ± 25.7 mm^3 and a median reduction of −12.5 mm^3 (95% CI, −15.5 to 10.5 mm^3), $P < .001$ compared with baseline.

Comment: This study demonstrates convincing regression of atherosclerosis in the coronary circulation with high-dose statin therapy. The study has some limitations in that there was no placebo control. Also, 22 patients were withdrawn because of ischemic events, and those patients may represent actual progression of atherosclerosis under the treatment protocol. Nevertheless, in the patients evaluated, coronary atherosclerosis was reduced with the high-dose statin therapy used in this study. There were minimal complications and intolerance associated with the drug. It seems clear that high-dose statin therapy is indicated for patients with significant coronary disease. There is no evidence to date, however, that such therapy will benefit patients with cerebrovascular or peripheral arterial disease. Those trials still need to be done.

Improvement in stroke mortality in Canada and the United States, 1990–2002

Quanhe Y, Botto L, Erickson JD, et al. Circulation 2006;113:1343-53

Conclusion: Stroke mortality has improved in the United States and Canada during the period of folic acid fortification of grain products. This suggests high homocysteine levels are independent risk factors for stroke and can be modified by folic acid fortification of grain products.

Summary: Folic acid fortification of grain products was fully implemented in the United States and Canada by 1998. Theoretically, this should result in a population-wide reduction in blood homocysteine levels. If it is assumed high homocysteine levels are an independent risk factor for stroke, this should result in a decrease in stroke mortality. The authors sought to address the hypothesis fortification of grain products with folic acid reduces stroke mortality in the United States and Canada. They used segmented log-linear regression analysis to evaluate stroke mortality trends before and after folic acid fortification of grain products. These data were compared with stroke mortality during the same period in England and Wales, where fortification of grain products with folic acid was not required.

Average blood homocysteine concentrations decreased and average blood folate concentrations increased in the United States after fortification. The previously observed decline in stroke mortality in the United States from 1990 to 1997 further accelerated from 1998 to 2002 in virtually all segments of the population. Overall, change varied from −0.3% (95% confidence interval [CI], −0.7 to 0.08) to −2.9 (95% CI, −3.5 to −2.3) per year ($P = .0005$). Sensitivity analysis indicated there were no other major recognized risk factor changes to account for the decreased trend of stroke-related deaths in the United States. In Canada, the fall in stroke mortality averaged −1.0% (95% CI, −1.4 to −0.6) per year from 1990 to 1997. This accelerated to −5.4% (95% CI, −6.0 to −4.7) per year from 1998 to 2002 ($P \leq .0001$). There was no change in stroke mortality in England and Wales from 1990 to 2002.

Comment: These data provide indirect evidence that stroke mortality can be modified by reducing overall homocysteine levels in the population. The sophisticated statistical methods used in this report make it unlikely that the findings presented represent chance alone. It is, however, unknown whether the reduction in stroke mortality is secondary to a decrease incidence of stroke or a decrease in the case fatality rate of stroke, and thus reflecting better stroke care rather than decreased stroke incidence.

Matrix metalloproteinase-8 and -9 are increased at the site of abdominal aortic aneurysm rupture

Wilson WRW, Anderton M, Schwalbe EC, et al. Circulation 2006;113:438-45

Conclusion: There is an increase of matrix metalloproteinase-8 (MMP-8) and MMP-9 at the site of aortic aneurysm rupture.

Summary: Processes that lead directly to abdominal aortic aneurysm (AAA) rupture are not well understood. The authors sought to study the role of MMPs and their inhibitors (TIMPs) in the cellular and proteolytic activity of ruptured AAAs. Biopsy specimens were obtained from the anterior wall of the aorta from 20 ruptured and 55 nonruptured AAAs. In 12 of the ruptured AAAs, biopsy specimens were taken from rupture site and analyzed for MMP-1, -2, -3, -8, -9, and -13. TIMP-1 and TIMP-2 were all

also quantified from each biopsy. Analysis was by enzyme-linked immunoabsorbent assay.

The biopsy specimens of the anterior sites showed no difference in MMPs or TIMPs concentrations in ruptured vs nonruptured aneurysms. MMP-8 and MMP-9 levels were elevated from the biopsy specimens of 12 ruptured sites compared with the 12 paired anterior wall biopsy sites (MMP-8, $P < .001$; MMP-9, $P = .01$). Other MMPs and TIMPs showed no difference. Expression of MMP-8 and MMP-9 was mediated by native mesenchymal cells. Expression was independent of inflammatory infiltrate.

Comment: The article suggests a final common pathway in the breakdown of extra cellular matrix in AAA rupture. The corollary, of course, is that inhibition of MMP-8 or MMP-9 activity could potentially decrease the risk of aneurysm rupture. Perhaps someday patients with aortic aneurysms unsuitable for repair will be treated with inhibitors of MMP-9 or MMP-8 in an attempt to prevent death from aneurysm rupture.

Asymptomatic central venous stenosis in hemodialysis patients

Levit RD, Cohen RM, Kwak A, et al. Radiology 2006;238:1051-6

Conclusion: In patients with a hemodialysis access graft and an asymptomatic central venous stenosis (CVS) of >50%, treatment of the CVS results in more rapid stenosis progression compared with a nontreatment approach.

Summary: The authors evaluated the natural history of >50% asymptomatic CVSs in hemodialysis patients. Outcome of serial treatment of CVS with percutaneous catheter-based techniques (PTA) was also evaluated. All patients in this study required maintenance procedures for their dialysis access.

Between 1998 and 2004, 35 patients (19 men, 16 women), with a mean age of 58.7 years, were found to have asymptomatic CVS of >50%. CVS was measured by using venograms obtained before and after PTA. Patients with arm swelling, multiple CVSs, or indwelling catheters, were excluded. CVS progression was calculated by comparing degrees of stenoses with serial venographic examinations.

The mean severity of CVSs before intervention was 71% (range, 50% to 100%), with 62% of lesions having associated collateral vessels. Twenty eight percent of CVSs were not treated. The mean degree of stenosis in the untreated group was 72% (range, 30% to 100%). Mean progression of stenosis in the untreated group was −0.8% point per day. No untreated CVS progressed to symptoms, stent placement, or developed additional CVS.

PTA was used to treat 62 CVS lesions (72%). The mean degree of stenosis in the treated group was 74% (range, 50% to 100%) before and 40% (range, 0% to 75%) after treatment. In the treated group, mean progression of CVS was 0.21% per day after treatment. Six of the 62 treated CVS lesions were monitored, with symptomatic escalation of the CVS as manifested by arm swelling, need for stent placement, or development of additional CVS lesions.

Comment: Treatment of an asymptomatic CVS in a dialysis patient is not a good thing. One is reminded of the old adage that it is wise to avoid poking a skunk. A major weakness of this study is that the patients were undergoing maintenance procedures for their dialysis access. We do not know if the CVS contributed to the need for the dialysis access maintenance. It would be interesting to know if there was a higher rate of repeat procedures for maintenance of dialysis access in patients with treated vs untreated CVS.

Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery

Schillinger M, Sabeti S, Loewe C, et al. N Engl J Med 2006;354:1879-88

Conclusion: At 6 months and 12 months, percutaneous angioplasty of superficial femoral artery stenoses with primary implantation of a self-expanding nitinol stent is superior to percutaneous angioplasty of superficial femoral artery stenoses with optional secondary stenting.

Summary: The authors evaluated whether primary implantation of a self-expanding nitinol stent in the superficial femoral artery yielded superior anatomic and clinical benefits compared with a policy of percutaneous transluminal angioplasty with stenting reserved as a secondary option. The study screened 252 patients for participation, of which 104 were eligible for randomization. These patients all had chronic limb ischemia and claudication due to stenosis or occlusion of the superficial femoral artery. Fifty-one patients underwent primary stent implantation, and 53 patients underwent angioplasty with secondary stent implantation.

The primary study end point was a rate of restenosis of at least 50% in the treated segment 6 months after intervention. Restenosis was determined by computed tomography angiography or digital subtraction angiography and was measured in the worst angiographic view of the narrowest stent segment or in the 10-mm segments proximal and distal to the treated superficial femoral artery segment. Secondary end points included restenosis as determined by duplex scanning at 3, 6, and 12 months. Rutherford's stage of peripheral arterial disease maximal walking capacity on the treadmill at 24 hours and at 3, 6, and 12 months were also determined. Amputation and death at 6 and 12 months were additional secondary end points. The ankle brachial index was measured at 24 hours, and at 3, 6, and 12 months.

The mean length of the treated arterial segment was 132 ± 71 mm in the primary stent group vs 127 ± 55 mm in the angioplasty/secondary stent group. In the secondary stent group, 17 patients (32%) had secondary stenting. At 6 months, the rate of restenosis on angiography was 43% in the angioplasty group and 24% in the primary stent group ($P = .05$). At 12 months, rates of restenosis were 63% in the angioplasty group and 37% in the primary stent group as determined by duplex scanning ($P = .01$). No amputations occurred in either group at 6 or 12 months, and one patient died in the primary stent group at 12 months. Patients in the stent group walked farther on the treadmill at 6 months (average distance, 363 vs 270 meters; $P = .04$) and at 12 months (average distance, 387 vs 267 meters; $P = .04$). At 12 months the ankle brachial index was higher in the stent group than in the angioplasty group ($P = .03$). The rate of stent fracture was 2%.

Comment: This study suggests that the primary use of nitinol stents may improve what is a relatively poor result of angioplasty and secondary stenting of the superficial femoral artery. Given that previous studies have suggested that an exercise program is as effective as or more effective than angioplasty of the superficial femoral artery, it is a shame that the authors did not include a control group in their trial. It would also have been nice to know whether the increased walking distance measured on the treadmill translated to an increased quality of life for the patients in this study. Nevertheless, it can be said that given the end points of this trial, the use of primary stenting with nitinol stents for angioplasty of the superficial femoral artery, was superior to selective stenting after angioplasty of the superficial femoral artery.

Homocysteine lowering with folic acid and B vitamins in vascular disease

The Heart Outcomes Prevention Evaluation (HOPE) Two Investigators. N Engl J Med 2006;354:1567-77

Conclusion: In patients with vascular disease, supplemental folic acid, vitamin B6, and B12 do not reduce the risk of major cardiovascular events.

Summary: In observational studies, higher homocysteine levels have been associated with increased rates of stroke and heart disease. It is known vitamins B6, B12, and folate can lower homocysteine levels. The purpose of this study was to determine whether the risk of major cardiovascular events in patients with vascular disease could be reduced with the use of supplemental vitamin therapy.

Patients who were aged ≥55 years and who had vascular disease or diabetes were randomly assigned either treatment with placebo or a combination of 2.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12. The study enrolled 5552 patients aged >55 years and monitored them for an average of 5 years. The primary end point was a composite of death from myocardial infarction, stroke, and other cardiovascular causes.

In the treatment group, mean plasma homocysteine levels decreased by 2.4 μm/L (0.3 mg/L). In the placebo group, mean plasma homocysteine increased by 0.8 μm/L (0.1 mg/L). Primary outcome end points occurred in 18.8% of the active therapy group (n = 519), and in 19.9% (n = 547) of the placebo group (relative risk [RR], 0.95; 95% confidence interval [CI], 0.84 to 1.07; P = .41). Compared with placebo, vitamin treatment did not decrease risk of death from cardiovascular causes (RR, 0.96; 95% CI, 0.81 to 1.13) or myocardial infarction (RR, 0.98; 95% CI, 0.85 to 1.14). More patients in the treated group were hospitalized for unstable angina (RR 1.24; 95% CI, 1.04 to 1.49). There were fewer strokes in the active treatment group than the placebo group (RR, 0.75; 95% CI, 0.59 to 0.97).

Subgroup analysis indicated no heterogenicity of treatment effect in patients from regions where food had mandatory supplementation of folate vs regions where food was not supplemented. There was no difference in treatment affects in patients with the top third of baseline homocysteine levels or in the patients with the top fifth of homocysteine levels. With adjustments for age, sex, and treatment assignment, baseline homocysteine level as a continuous measure was a predictor of cardiovascular events.

Comment: Multiple trials have now demonstrated a lack of efficacy of supplemental vitamin therapy to decrease cardiovascular events. This is despite documented lowering of homocysteine levels by the vitamin therapy. This discordance between epidemiology and results of clinical trials is similar to that noted for estrogen and antioxidant vitamins. It may be that the epidemiologic data of homocysteine are confused by confounding variables that cannot be completely adjusted for in multivariable analysis. It may, however, simply be that homocysteine is a marker but not a cause of vascular disease.

Massive pulmonary embolism

Kucher N, Rossi E, DeRosa M, et al. Circulation 2006;113:577-82

Conclusion: Mortality of pulmonary embolism in patients with massive pulmonary embolism (PE) is not reduced by thrombolysis or embolectomy. There does appear to be reduced mortality in patients with massive PE who have placement of inferior vena cava filters.